

PROPOSAL FOR USE OF TWO CONCENTRATIONS FOR METAMIZOL TO INTRADERMAL TESTING

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Abstract

Metamizol, a pyrazolone derivative, is commonly implicated in IgE-mediated allergic reactions. Skin tests have different sensitivity in drug allergy diagnosis and false positive or false negative results render their interpretation difficult, especially because the ranges of the tested concentrations have not been adequately investigated in all drugs. The objective of our study was to determine the non-reactive concentrations for metamizol in healthy subjects using prick and intradermal tests.

We studied the wheal and flare response to prick and intradermal tests in 20 Caucasian nonallergic volunteers for metamizol. We selected more clustered concentrations that resulted from decimal dilutions, identical for both prick and intradermal testing (500, 250, 100, 50, 25, 10, 5 and 1 mg/mL). For intradermal testing we focused on reading wheal/initial wheal ratio (RW/IW) at different metamizol concentrations.

For prick testing the maximal concentration which did not produce wheal and flare was 500 mg/mL. For intradermal tests, we defined some test concentrations (C) important in the interpretation: C1 represents the highest concentration for which the test is not modified (RW/IW ratio ≤ 1); C2 represents the highest concentration for which the test is modified but the RW/IW ratio is < 2 ; Cmax represents the concentration for which half of the subjects surpass positivity criteria $RW/IW \geq 2$. For metamizol C1 is 5 mg/mL, C2 is 50 mg/mL and Cmax is 250 mg/mL. Using two reading concentrations, C1 and C2, it might be reduced the number of errors due to false positive and false negative results and it might improved the interpretation of intradermal tests.

Rezumat

Metamizolul, un medicament din clasa pirazolonelor, este frecvent implicat în reacții alergice IgE-mediate. Testele cutanate alergologice la medicamente au sensibilitate diferită, ceea ce face ca interpretarea lor să fie dificilă. Rezultatele fals pozitive sau fals negative pot fi generate de utilizarea unor concentrații-test insuficient validate la ora actuală pentru toate medicamentele. Obiectivul studiului de față a constat în determinarea concentrației maxime non-reactive pentru metamizol pentru testarea cutanată *prick* și intradermică. Am studiat răspunsul de tip papulă și eritem (*wheal and flare*) la testarea cutanată *prick* și intradermică la 20 de voluntari caucazieni non-alergici la metamizol. Am

selectat o serie de concentrații mai apropiate decât cele obținute prin diluții zecimale, care s-au aplicat atât pentru testarea *prick* cât și intradermică (500, 250, 100, 50, 25, 10, 5 și 1 mg/mL). Pentru testul intradermic am urmărit evoluția raportului între diametrul papulei de injecție și diametrul papulei de citire (RW/IW) în funcție de diferite concentrații ale metamizolului.

Pentru testul cutanat *prick* concentrația maximală care nu produce papulă și eritem este de 500 mg/mL. Pentru testul intradermic am definit unele concentrații (C) importante pentru interpretarea diagnostică: C1 reprezintă cea mai înaltă concentrație pentru care aria de test nu se modifică ($RW/IW \leq 1$), C2 este cea mai înaltă concentrație la care aria de test se modifică, dar raportul nu se dublează ($RW/IW < 2$), iar Cmax reprezintă concentrația la care jumătate dintre subiecți întrunesc criteriile de pozitivitate pentru un test intradermic ($RW/IW \geq 2$). Pentru metamizol, C1 este de 5 mg/mL, C2 este de 50 mg/mL, iar Cmax este de 250 mg/mL. Utilizând simultan două concentrații diferite, C1 și C2, se poate reduce numărul de erori generate de reacțiile fals pozitive sau fals negative obținute la interpretarea testului intradermic.

Keywords: allergy, intradermal test, metamizol, drug concentration

Introduction

Metamizol is a non-opioid analgesic and antipyretic drug used in both paediatric and adult patients. It belongs to the family of pyrazolone drugs and it is in clinical use since 1922. Although in some countries metamizol is banned because of the high risk of agranulocytosis [19], in others it is the leading analgesic and antipyretic drug, having a significant amount of sales [19, 1].

Metamizol is effective in postoperative analgesia [15, 16] and has opiate sparing effect [27], though it is used in improving cancer pain management [32] and it is one of the most frequently used drugs in palliative care [23]. Metamizol is synergic with tramadol in improving the postoperative analgesia [22]. In experimental models using the strategy of combining tramadol with ketamine and baclofen it was also observed a reduction of nociception [5], and in a clinical study ketamine and remifentanyl was combined [30]. Metamizol is effective as symptomatic antipyretic agent [24, 31], and is one of the most commonly used drugs in acute primary headaches [26]. It is widely prescribed in hospital setting [1] and also is used as over-the-counter analgesic [18]. In Romania metamizol is used on a large scale as over-the-counter analgesic, in the hospital setting and also in the ICU (intensive care unit). It has many commercial names worldwide: Dipyron[®], Algocalmin[®], Feverall[®], Novalgin[®], Nolotil[®] and others [28].

Administration of pyrazolones, including metamizol can cause adverse reactions of many types. Some reactions result from the inhibition

of cyclooxygenase in patients with ASA (acetylsalicylic acid) triad or chronic urticaria [4]. Other reactions have an immunologic underlying mechanism, and at least in part are IgE mediated [14]. In Spain, pyrazolones are the second cause of IgE mediated reactions to drugs, only preceded by betalactam antibiotics [13].

In the subset of IgE-mediated reactions to drugs prick and intradermal skin tests represent an important diagnosis tool, with a role in identifying the agent causing allergy. Nevertheless, testing protocols to drugs and test concentrations are still a matter of controversy [2]. Different concentrations are used by different groups, and this regards mainly to intradermal tests concentrations. It is established that intradermal tests are prone to give false positive results more often than prick tests, especially for high drug concentrations [2, 3].

We designed the present study in order to define the concentrations of metamizol not associated with a false positive reaction in non-allergic healthy volunteers, to use more clustered concentrations than those resulting from decimal dilutions and to propose the use of two concentrations to better define the maximum concentration that is not associated with a false positive reaction.

Materials and methods

Tested substances, concentrations

With the approval of Research Ethics Committee of the University of Medicine and Pharmacy "Iuliu Hațieganu" Cluj-Napoca the prick and intradermal skin tests were performed on healthy adult volunteers using a commercially available solution of metamizol. We tested Algocalmin® (Zentiva, Romania), with the following composition: 2 mL injectable solution, containing 1.05 g of metamizol natrium monohydrate and water for injections. The substance we tested is a commercial product used frequently in the ICU setting, supplied in the test day, sealed, with attached documentation. The maximum concentration used in the tests was the concentration of the drug in the commercial vial. Normal saline solution (0.9% NaCl) was used to dilute the commercial substance. The concentrations for testing skin reactivity to metamizol were 500 mg/mL, 250 mg/mL, 100 mg/mL, 50 mg/mL, 25 mg/mL, 10 mg/mL, 5 mg/mL, and 1 mg/mL. The pH of each dilution was measured with the ChemCadet pH meter that showed a slightly increase from 6.044 for 1 mg/mL to 6.733 for 500 mg/mL. All these concentrations were applied in prick tests and also in intradermal tests.

Subject group

A total of 20 healthy Caucasian volunteers, aged between 23 and 35 (average 28.9 years) participated in the study, giving the informed written consent. The group included 11 males (55%) and 9 females (45%) none of whom were pregnant or breast feeding. No subjects with atopic background, allergic diseases (asthma, rhinitis) or other chronic diseases were included. The subjects were not taking steroid medication, antihistamines or antidepressants. All the subjects presented multiple previous exposures to metamizol with no adverse reactions suggestive for immediate-type hypersensitivity or other adverse reactions to metamizol.

Test performance technique and interpretation

The skin tests were performed in conformity with published recommendations [21] and according to the methodology described for skin testing in drug allergy [6]. Our study was conducted in a prospective, double blind manner – one allergologist experienced in skin testing performed the tests with the prepared dilutions, whilst another allergologist who did not know the testing concentrations established the mean diameter of the wheals. For prick tests, we put solution drops of different concentrations of the investigated substance on the anterior forearm of the subject, and then we pricked the skin with a prick needle (Stallerpointe, Stallergenes, Antony, France) in the middle of each drop, with no bleeding. For intradermal tests, we injected intradermally a volume of 0.02-0.03 mL, through a 29 ½ gauge needle which resulted in an injection bleb (wheal) of 4 mm diameter. The chosen testing area was also the anterior forearm. Evaluation of skin reactivity of tested subjects was performed comparing with controls: for prick tests we used as negative control phenol saline glycerol (Stallergenes) and as positive control histamine 1% (Stallergenes). As negative control for the intradermal test we used a diluent volume which, when injected into the skin, should produce an initial wheal with a 4 mm diameter.

The interpretation of the prick test was considered positive in the case of the appearance within 20 minutes of a wheal with a diameter over 3 mm, compared to the negative control, or with a diameter equal / superior to 1/2 of positive control wheal. For intradermal tests, positivity criterion was the appearance of a wheal of at least 8 mm diameter within 20 minutes, or the doubling of the injection wheal [21].

Statistical method

For the intradermal tests, the relation between the reading wheal and initial wheal diameter ratio (RW/IW) and the concentrations of the drug was analysed using logarithmic models and Pearson correlation coefficient (Excel software, 2003, Microsoft Corporation, Seattle, USA).

Results and discussion

For prick testing no subject developed any wheal exceeding or equal to 3 mm during a 20 minutes time interval, regardless of the used concentration. For metamizol, even at the maximum concentration, no wheal or flare were observed. No prick test passed positivity criteria. Skin reactivity was considered normal, with usual reaction to histamine 1% used as a positive control. All subjects developed wheals with diameters between 4 and 7mm, surrounded by erithema of 15 to 25 mm. At the negative control no subject presented any wheal or flare.

For intradermal testing, skin reactivity was appreciated as normal in the case of the negative control (saline physiological solution) for all the subjects, and the initial wheal diminished or vanished after 20 min interval. The positivity criteria for intradermal testing, according to SFAR (Société Française d'Anesthésie et de Réanimation) [21] consists in the doubling of the initial wheal within 20 min from injection. In this case, the ratio between the reading wheal and the initial wheal (RW/IW) should be at least 2 to 1. During the study we observed the RW/IW ratio at different metamizol concentrations. We defined some concentrations, considering that each has a possible diagnostic implication. The first concentration, designated as C1, is the highest concentration at which the testing area does not modify, when the RW/IW ratio is less than or equal to 1. The second concentration, designated C2, is the highest concentration at which the RW/IW ratio is less than 2, and the wheal did not double for any tested subject. Any concentration exceeding C2 starts producing positivity for the intradermal test. These positive reactions of healthy non-allergic subjects are, in fact, false positive reactions, by a nonspecific effect. The third concentration, designated as Cmax, is defined as the concentration at which at least 50% of the subjects had a positive reaction to the test. Values C1, C2, Cmax are presented in table I.

Table I
Correlation between the reading wheal and initial wheal ratio (RW/IW) and metamizol concentration

Metamizol Concentration (mg/mL)	RW / IW																	Total
	0	0.5	0.75	1	1.125	1.25	1.375	1.5	1.625	1.75	1.875	2	2.125	2.25	2.375	2.5	2.625	
Number of patients																		
1	18		1	1														20
C1 5	16		3	1														20
10	9	2	5	2		2												20
25		1	7	6	1	2	1	1	1									20
C2 50			1	3		6	1	4	4	1								20
100						2	1	1	5	7								20
C3 250								2		4	1	7	2	2	1			20
500										1	3	3	1	2	3	3	1	20
Total	43	3	17	13	1	12	3	8	10	13	1	14	3	4	4	3	3	160

RW/IW = reading wheal to initial wheal ratio; C1 = the highest concentration at which $RW/IW \leq 1$; C2 = the highest concentration at which $RW/IW < 2$; C3 = the concentration at which 50% of subjects registered $RW/IW > 2$

At the concentration 500 mg/mL for 19 subjects (95%), the RW/IW ratio is greater or equal to 2, so the wheal doubles and the test is positive. At 250 mg/mL the wheal doubles for 65% of the subjects, and at 100 mg/mL for only 20% of these. At 50 mg/mL the injection wheal did not double for any tested subject, the RW/IW ratio being less than 2. Even if at 50 mg/mL the wheal did not double, the testing area was modified for 75% of the subjects, without meeting the positivity criteria. At 5 mg/mL the testing area did not modify, the RW/IW ratio being less than or equal to 1. This data is presented in table I. For metamizol, the RW/IW ratio increases in a non-linear correlation with the substance concentration of the injected solution. The highest the concentration of metamizol is, the more intense the skin reaction is (Figure 1). We searched for the mathematical model that best fitted the skin response. As it can be seen from Figure 1 it results a logarithmic relation. Hence, there was a strong correlation between the RW/IW ratio and the concentration of drug ($r = 0.9$ and $p < 0.01$).

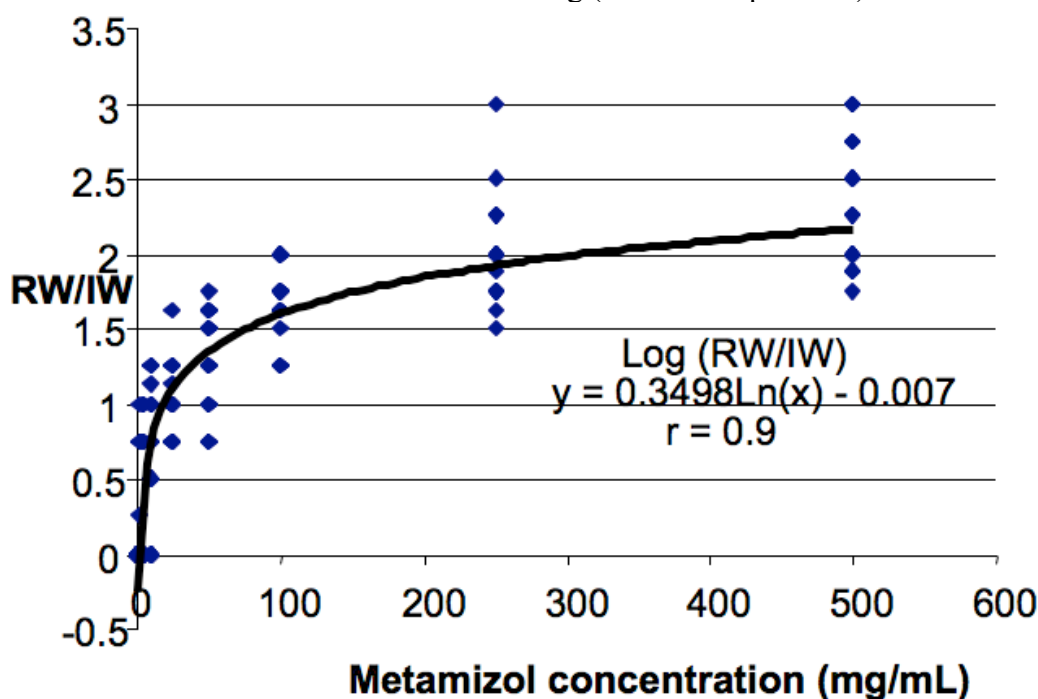


Figure 1

Correlation between the RW/IW ratio and the concentration for metamizol
 RW/IW = reading wheal to initial wheal ratio; C1 = the highest concentration at which $RW/IW \leq 1$; C2 = the highest concentration at which $RW/IW < 2$; C3 = the concentration at which 50% of the subjects registered $RW/IW > 2$

The flare around the injection wheal was also evaluated 20 min after the intradermal administration. For metamizol, at C_{max} (250 mg/mL) a number of 9 subjects (45% of the group) presented a flare with the diameter of 10-15 mm. At C1 and C2 no subject presented any flare (Table II).

Table II
Correlation between the concentration of metamizol and the flare dimension

Metamizol	Flare (mm)								Total
	0	10	12	14	15	16	17	20	
Concentration (mg/mL)	Number of patients								
C1	1	20							20
	5	20							20
	10	20							20
C2	25	20							20
	50	20							20
	100	18	2						20
C3	250	11	4	3	1				20
	500	5	2	1	5	1	1	5	20
	Total	134	8	4	1	6	1	1	5

RW/IW = reading wheal to initial wheal ratio; C1 = the highest concentration at which $RW/IW \leq 1$; C2 = the highest concentration at which $RW/IW < 2$; C3 = the concentration at which 50% of the subjects registered $RW/IW > 2$

There are no internationally accepted guidelines on skin testing to drugs regarding the threshold concentrations, even few accepted criteria for the performance technique and interpretation of skin tests are published [2, 6, 17, 21]. ENDA (European Network on Drug Allergy) members currently test patients with a number of drugs to gain and publish experience on the value of skin testing under different conditions [3].

For some substances there are strong recommendations referring to the concentrations that are used in intradermal tests. Such recommendations are found in SFAR guidelines for specific anaesthetic medication [21], or in ENDA position paper for diagnosis of immediate allergic reactions to β -lactam antibiotics [29].

Threshold concentrations necessary for the interpretation of skin tests in the field of drug allergy can be determined by testing healthy controls, in order to establish the maximum non-reactive concentrations for each substance. For skin testing, the criteria for positivity are based on dilutions of drugs that do not cause wheal and flare reactions in subjects without history of reaction. There are ethical difficulties in testing large numbers of non-reactors simply to validate a test [10]. Research studies, which evaluate skin reactivity to different drug concentrations are performed on small groups of subjects, as described in several papers regarding NMBAs (neuromuscular blocking agents) [20, 7].

Prick and intradermal skin tests are used for establishing the drug responsible for anaphylactic reactions in the perioperative period, with a similar efficacy. The agreement between these two paired test techniques is 93%, without significant statistical differences [11]. Nevertheless, each technique has certain advantages. Prick test is quicker, simpler to administer, less traumatizing, more specific and easier to apply to children than intradermal test, but this last one is more sensitive and reproducible than the prick test [25]. Using both types of tests improves predictability by 67% [11], so the degree of confidence is higher for the patient. In the case of a negative or an inconclusive prick test, it is recommended to continue the investigation with an intradermal test [8].

Intradermal tests are, in general, more exposed to false positive results than the prick test, because of the use of too high test concentrations. Using too high dilutions might be a source of false negative results [11]. In this case, false negative results could have dramatic consequences when exposing the patient to tested substance [8]. A false positive result is less dangerous than a false negative result [11]. Criteria for positivity differ slightly among authors [21, 2]. According to the criterion defined by the ENDA, an intradermal test is considered positive when the size of the initial wheal diameter of 3 mm increases by 3 mm or more after 15-20 min and is associated with a flare [3]. This criterion has been employed first in the diagnosis of penicillin allergy and then extrapolated to other drugs [2]. Working in an allergeo-anaesthesia setting, we chose the methodology of test performance and the interpretation recommended by SFAR for drugs used in the perioperative period [21].

For metamizol, the commercial solution with a concentration of 500 mg/mL and all other concentrations did not produce wheal or flare at any subject in the prick test area.

According to our results, skin prick tests can be performed on the undiluted solution that has a concentration of 500 mg/mL for metamizol, without any false positive reaction.

In the case of the intradermal test, results are very interesting, and in our opinion the interpretation of these tests should be done more cautiously. Using serial dilutions rather than a single concentration would increase the diagnostic value of the intradermal testing [11]. Our team defined some test concentrations with an important role in the interpretation of the intradermal test, to account for the dimension of the reading wheal (RW) as compared with the dimension of the injection wheal (IW).

C1 represents the highest drug concentration for which the testing area is not modified, that is, for which the RW/IW ratio is less than or equal

to 1. According to our observations, for metamizol this concentration is 5 mg/mL. At these concentration values when reading the test in nonallergic subjects one can observe the diminishing or lack of modification of wheal formed when injecting. Also, at these values, no subject presented any flare around the injection point. So, C1 is appropriate for the definition above [10, 3] for maximal nonreactive concentration. C2 represents the concentration which, when surpassed, implies the risk of occurrence of false positive reactions, and is the highest concentration at which RW/IW ratio is less than 2. In this case, the test area modifies, but the injection wheal does not double, so that the test cannot be interpreted with certitude as positive. A flare appears also at some tested subjects. At this concentration, we enter a zone of inconclusive reactions, with a behaviour difficult to interpret. Such situations can be observed for metamizol at a concentration of 50 mg/mL. The optimal test concentration has to be determined for each drug. This concentration has to show positive results in patients with drug hypersensitivity, and a specificity higher than 95% should be expected. Only a skin test reaction to a drug tested at a concentration that does not cause an unspecific irritative reaction in controls is edifying for drug hypersensitivity [3]. Our results suggest that for metamizol the optimal test concentration could be in the range 5 mg/mL-50 mg/mL, and in this case we avoid false positive results ($1 \leq \text{RW/IW} < 2$).

At **Cmax**, half of the reactions surpass positivity criteria if we account for doubling of the injection wheal ($\text{RW/IW} \geq 2$), and a flare can be observed in most of the subjects. In our opinion, at these concentrations there are frequently registered false positive reactions, leading to considering non-allergic individuals as being positive. For metamizol this concentration is 250 mg/mL. The challenge is to avoiding both false positive reactions, as well as false negative reactions, which are more dangerous than the first ones [10].

Using C1 and C2 in parallel as reading concentrations could reduce the number of errors due to false positive results, and respectively false negative ones, and to improve the interpretation of intradermal tests.

The patients with modified testing area but not reaching the criteria for positivity are advised about the tested drug [11]. In our case, a doubtful reaction, especially with C1, should be reported and a therapeutical alternative should be found. The skin area used for the test (the forearm) can influence the results, which could be different if using other areas, for example the back [8]. One other problem could arise from using commercial products instead of purified substances, because of some possible irritating effects of the excipients. The correlation between the skin reactivity and the

drug concentration measured by HPTLC (high performance thin layer chromatography) in the skin layers could represent a new research challenge, knowing that this method allows to determine substances in biological matrices (blood, urine, tissue) [9]. The testing of commercial products frequently used in the ICU has a practical importance, because these substances will be usually used for therapy purposes. Skin tests represent a very important diagnostic tool in perianaesthetic allergy [21, 8]. Optimization and validation of some concentrations for interpretation of these tests have a great importance, especially because in immediate drug allergy diagnosis no methods (skin tests, radioimmunoassays, other) have an absolute value, and it is hard to establish which test is more accurate for each case [12].

Conclusions

Our observations favour the utilization of two different reading concentrations for intradermal tests to metamizol. These concentrations emerge from serial dilutions rather than decimal ones. These might have the role to reduce the risk of false positive reactions (C1), or false negative ones (C2), with an impact upon the prognostic of the patient risk of drug induced anaphylaxis. We consider, nevertheless, that the information we provided for metamizol is important and validation must come from other research groups as well.

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References

1. Braga TB, Pfaffenbach G, Weiss DP, Barros MB, Bergsten-Mendes G. Point prevalence of drug prescriptions for elderly and non-elderly inpatients in a teaching hospital. *Sao Paulo Med J* 2004; 122: 48-52
2. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug sensitivity. *Allergy* 2002; 57: 45-51
3. Brockow K, Romano A. Skin tests in the diagnosis of drug hypersensitivity reactions. *Curr Pharm Des* 2008; 14: 2778-2791
4. Campi P, Manfredi M, Severino M. IgE-mediated allergy to pyrazolones, quinolones and other non- β -lactam antibiotics. In: Pichler WJ editor. Drug hypersensitivity. Basel: Karger, 2007; 216-232
5. Cucuiet S, Dogaru G, Bild VN, Dogaru MT. Modulation of tramadol antinociception by ketamine and baclofen in mice. *Farmacia* 2008; 6: 675-691
6. Demoly P, Piette V, Bousquet J. In vivo methods for study of allergy: skin tests, technique and interpretation. In: Adkinson NF Jr, Yunginger JW, Busse WW, Bochner BS, Holgate TS, Simons FER, editors. Middleton's Allergy, principles and practice (6th ed), Philadelphia, Pennsylvania: Mosby, Inc. 2003; 631-643

7. Dhonneur G, Combes X, Chassard D, Merle JC. Skin sensitivity to rocuronium and vecuronium: a randomized controlled prick-testing study in healthy volunteers. *Anesth Analg* 2004; 98: 986-989
8. Ebo DG, Fisher MM, Hagedorens MM, Bridts CH, Stevens WJ. Anaphylaxis during anaesthesia: diagnostic approach. *Allergy* 2007; 62: 471-487
9. Ebrahim Z.A.J., Bălălaşu D, Baconi DL, Guțu CM, Ilie M. HPTLC method for the assay of tramadol and pentazocine from mixtures. *Farmacia* 2011; 59(3): 381-387
10. Fisher MM, Doig GS. Prevention of anaphylactic reactions to anaesthetic drugs. *Drug Safety* 2004; 27: 393-410
11. Fisher M, Bowey CJ. Intradermal compared with prick testing in the diagnosis of anaesthetic allergy. *Br J Anaesth* 1997; 79: 59-63
12. Fisher MM, Baldo BA. Anaphylaxis during anaesthesia: current aspects of diagnosis and prevention. *Eur J Anaesth* 1994; 11: 263-284
13. Gamboa PM, Sanz ML, Caballera MR, Antepara I, Urrutia I, Jauregui I. Use of CD63 expression as a marker of in vitro basophil activation and leukotriene determination in metamizol allergic patients. *Allergy* 2003; 58: 312-317
14. Gómez E, Blanca-Lopez N, Torres MJ, Requena G, Rondon C, Canto G, Blanca M, Mayorga C. Immunoglobulin E-mediated immediate allergic reactions to dipyrone: value of basophil activation test in the identification of patients. *Clin Exp Allergy* 2009; 39: 1217-1224
15. Grundmann U, Wörnle C, Biedler A, Kreuer S, Wrobel M, Wilhelm W. The efficacy of the non-opioid analgesics parecoxib, paracetamol and metamizol for postoperative pain relief after lumbar microdiscectomy. *Anesth Analg* 2006; 103: 217-222
16. Kampe S, Warm M, Landwehr S, Dagtekin O, Haussmann S, Paul M, Pilgram B, Kiencke P. Clinical equivalence of IV paracetamol compared to IV dipyrone for postoperative analgesia after surgery for breast cancer. *Curr Med Res Opin* 2006; 22: 1949-1954
17. Kroigaard M, Garvey LH, Gillberg L, Johansson SGO, Mosbech H, Florvaag E, Scandinavian clinical practice guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. *Acta Aneasthesiol Scand* 2007; 51: 655-670
18. Lefterova A, Getov I. Study on consumers' preferences and habits for over-the-counter analgesics use. *Cent Eur J Public Health* 2004; 12: 43-45
19. Levy M. Hypersensitivity to pyrazolones. *Thorax* 2000; 55: S72-S74
20. Levy JH, Gottge M, Szlam F, Zaffer R, McCall C. Wheal and flare responses to intradermal rocuronium and cisatracurium in humans. *Br J Anaesth* 2000; 85: 844-849
21. Mertes PM, Laxenaire MC, Lienhart A, and the working group of the SFAR and Aberer W, Ring J, Pichler WJ, Demoly P, for ENDA and the EAACI interest group on drug hypersensitivity. Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. *J Invest Allergol Clin Immunol* 2005; 15: 91-101
22. Montes A, Warner W, Puig MM. Use of intravenous patient-controlled analgesia for the documentation of synergy between tramadol and metamizol. *Br J Anaesth* 2000; 85(2):217-223
23. Nauck F, Ostgathe C, Klaschik E, Bausewein C, Fuchs M, Lindena G, Neuwöhner K, Schulenberg D, Radbruch L; Working Group on the Core Documentation for Palliative Care Units in Germany. Drugs in palliative care: results from a representative survey in Germany. *Palliat Med* 2004; 18: 100-107
24. Oborilová A, Mayer J, Pospisil Z, Korístek Z. Symptomatic intravenous antipyretic therapy: efficacy of metamizol, diclofenac, and propacetamol. *J Pain Symptom Manage* 2002; 24: 608-615
25. Romano A, Demoly P. Recent advances in the diagnosis of drug allergy. *Curr Opin Allergy Clin Immunol* 2007; 7: 299-303
26. Ruiz Jr FB, Santos MS, Siqueira HS, Cotta UC. Clinical features, diagnosis and treatment of acute primary headaches at an emergency center: why are we still neglecting the evidence? *Arq Neuropsiquiatr* 2007; 65: 1130-1133

27. Tempel G, von Hundelshausen B, Reeker W. The opiate-sparing effect of dipyron in postoperative pain therapy with morphine using a patient-controlled analgesic system. *Intensive Care Med* 1996; 22: 1043-1047
28. The Merck Index. Whitehouse Station, Merck Research Laboratories, 1996
29. Torres MJ, Blanca M, Fernandez J, Romano A, de Weck A, Aberer W, et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy* 2003; 58: 961-972
30. Truță E, Vărtic M, Cristea AN. Clinical study regarding preemptive analgesic effect of ketamine and remifentanyl in laparoscopic cholecystectomy. *Farmacia* 2011; 59 (2): 239-245
31. Yilmaz HL, Alparslan N, Yildizdas D, Bayram I, Alhan E. Intramuscular dipyron *versus* oral ibuprofen or nimesulide for reduction of fever in the outpatient setting. *Clin Drug Investig* 2003; 23: 519-526
32. Zernikow B, Smale H, Michel E, Hasan C, Jorch N, Andler W. Paediatric cancer pain management using the WHO analgesic ladder-results of a prospective analysis from 2265 treatment days during a quality improvement study. *Eur J Pain* 2006; 10: 587-595

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